## REMARKS

The specification has been amended to capitalize trademarks and remove reference to embedded hyperlinks.

Applicants have cancelled Claims 1-3 and 9-10 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 4-8 to delete reference to the Figures. Claims 4-6 are amended to delete elements (c) and (d). Claims 4 and 5 are amended to include the limitation "wherein said isolated polypeptide is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue." Applicants have amended Claim 4 to be in independent form, and have amended Claims 5 and 12 to depend from Claim 4. Claim 13 is amended to replace the term "epitope tag" with the term "tag polypeptide." New Claims 14-17 have been added.

Applicants submit that no new matter was added by the amendments, and that support for the amendments can be found throughout the specification. Support for the amendments to Claims 4 and 5 can be found, for example, in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification. Support for the amendments to Claim 13 can be found, for example, at paragraph [0229]. Support for new Claims 14-17 can be found, for example, in the claims as originally filed and paragraphs [0336], [0362], [407], and Example 18 starting at paragraph [0529].

Claims 4-8, and 11-17 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed February 1, 2005. For the reasons set forth below, Applicants respectfully traverse.

**Correction of Inventorship under 37 CFR §1.48(b)**

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

**Specification**

The disclosure was objected to by the PTO as containing embedded hyperlinks and/or other form of browser-executable code. The specification has been amended to remove reference to embedded hyperlinks. The specification has been further amended to indicate trademarks by capitalizing the trademarks and providing generic terminology.

**Rejection under 35 U.S.C. §101 – Utility**

The PTO has rejected Claims 1-13 because the claimed invention is not supported by a specific and substantial asserted utility. The PTO asserts that the disclosed uses for PRO polynucleotides and polypeptides in general in the specification are not specific to the PRO1753 polynucleotide. One of the asserted utilities for the claimed polypeptides is use as a diagnostic tool based on the data that PRO1753 cDNA is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue. The PTO has rejected this utility because the specification provides no information regarding absolute values of the differences in transcript levels, and no information on the level of expression, activity, or role of the PRO1753 polypeptide in cancer.

The PTO cites Haynes *et al.* (Electrophoresis, 19(11):1862-71 (1998)) and Hancock (J. Proteome Res., 3(4):685 (2004)), as support for the assertion that "the art demonstrates that increased transcript levels do not *necessarily* correlate with increased polypeptide levels." Office Action at 4 (emphasis added). The PTO also states that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The PTO cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) to support the conclusion that not all genes with increased expression in cancer have a known or published role in cancer. The PTO cites Wang *et al.* (Trends in Pharmacol. Sci., 17(8):276-9 (1996)) for the assertion that differential expression is only the first of many steps required in the discovery of a novel pharmacological target. Finally, the PTO states that although structural similarity can serve to classify a protein as related to other known proteins, this classification is insufficient to establish a function or biological significance for the protein. The PTO relies on an article by Henikoff *et al.* (Science, 278:609-614 (1997)) to support the assertion that "one skilled in the art would not accept mere homology as establishing a function of protein because gene products

may acquire new specificities, altered recognition properties, or modified functions." Office Action at 4-6.

Based on these references, the PTO states that the specification fails to disclose enough information about the invention to make its usefulness immediately apparent to those in the field. The PTO asserts that "the skilled artisan would not know if PRO1753 polynucleotide transcript levels or PRO1753 polypeptide expression could, should, or would be upregulated, down-regulated, or unchanged in cancer." Office Action at 6. The PTO concludes that further research would be needed to identify or confirm a "real world" context of use for the claimed invention.

Applicants respectfully disagree.

*Utility – Legal Standard*

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating

that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

*Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient*

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test

> results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

**Substantial Utility**

*Summary of Applicants' Arguments and the PTO's Response*

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed polypeptides have utility as diagnostic tools for cancer, particularly esophageal cancer. Applicants are not asserting

that the claimed polypeptides necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1753 polypeptide is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the level of mRNA for the PRO1753 polypeptide is increased in esophageal tumor, compared to normal esophageal tissue, it is likely that the PRO1753 polypeptide is differentially expressed in esophageal tumor and is therefore useful as a diagnostic tool to distinguish tumor from normal tissue.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that it provides no information regarding the level of expression, activity, or role of the PRO1753 polypeptide in cancer;

2. The PTO cites Hu *et al.* and Wang *et al.* for the assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels, and that differential expression is only the first of many steps required in the discovery of a novel pharmacological target;

3. The PTO cites Haynes *et al.* and Hannocock *et al.* to support its position that increased transcript levels do not *necessarily* correlate with increased polypeptide levels;

4. The PTO cites Henikoff *et al.* for the proposition that mere homology does not establish the function of a protein. The PTO concludes that further research needs to be done to use PRO1753 as a cancer diagnostic tool.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, (attached as Exhibit 1) which establishes the reliability of the data of Example 18. Second, knowing the biological significance

of the data, or the role of PRO1753 in cancer, is not necessary to use the claimed polypeptides as cancer diagnostic tools. Third, Applicants submit that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO1753 protein is likely differentially expressed in certain tumors. This provides utility for the PRO1753 and related proteins as cancer diagnostic tools. Fourth, Applicants do not rely on the function of the encoded polypeptides for utility for the claimed polypeptides.

Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants ' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute or statistical certainty.**

*Applicants have established that the Gene Encoding the PRO1753 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool*

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1753 polypeptide in certain tumors compared to their normal counterparts is insufficient because the specification provides no information regarding absolute values of the differences in transcript levels. Applicants also address the PTO's argument that the data do not establish a utility because the specification does not disclose any information on the level of expression, activity, or role of the PRO1753 polypeptide in cancer. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed polypeptides related to the PRO1753 polypeptide.

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the

counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples.

He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that a lack of known role for PRO1753 in cancer does not prevent its use as a diagnostic tool for cancer. The fact that there is no known translocation or mutation of PRO1753, for example, is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1753 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides. (*See, e.g.,* U.S. Patent No. 6,414,117 and U.S. Patent No. 6,124,433, attached hereto as Exhibits 2 and 3.)

The PTO relies on two references to support its assertion that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The PTO cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) for support for the conclusion that not all genes with increased expression in cancer have

a known or published role in cancer. The PTO cites Wang *et al.* (Trends in Pharmacol. Sci., 17(8):276-9 (1996)) for the assertion that differential expression is only the first of many steps required in the discovery of a novel pharmacological target. Applicants respectfully submit that these references do not satisfy the PTO's burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level an a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker. Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an

actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease.

Applicants submit that a lack of known role for PRO1753 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but they can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1753 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

In Wang, the authors outline a strategy for using mRNA differential display for the discovery of novel pharmacological targets. They state that the use of mRNA differential display for the isolation of novel genes associated with disease processes will no doubt facilitate discovery of novel pharmaceutical targets. *See* Wang at 279. However, they state that it is the first of many steps in the process, and that characterization of the functions of the gene as well as validation of the importance of the gene in disease processes. *Id.*

As with the Hu reference, nothing in Wang is contrary to Applicants' assertion that differentially expressed genes can be used as molecular markers of cancer. Wang speaks only of the additional steps needed to develop a *pharmacological target.* Contrary to the PTO's assertions, nowhere does Wang teach that differentially expressed genes cannot be used as molecular markers for cancer. As an aside, it is worth noting that of the ten steps outlined by Wang in Figure 1, Applicants have completed the equivalent of steps 1-9, as the Applicants have obtained and characterized the full-length cDNA. Thus, Wang does not refute the Applicants' assertion that the PRO1753 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Hu and Wang are not sufficient to prove that a person of skill in the art would have a reasonable doubt that a gene

differentially expressed in certain tumors can be used as a diagnostic tool since neither reference addresses this issue.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1753 cDNA between esophageal tumor tissue and normal esophageal tissue, respectively. Therefore, it follows that expression levels of the PRO1753 gene can be used to distinguish esophageal tumor tissue from normal esophageal tissue. The PTO has not offered any significant arguments or evidence to the contrary. As Applicants explain below, it is more likely than not that the PRO1753 polypeptide can also be used to distinguish esophageal tumor tissue from normal esophageal tissue.

*Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein*

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence that of differential expression of the mRNA for the PRO1753 polypeptide in esophageal tumor, it is likely that the PRO1753 polypeptide is differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response, the PTO cites Haynes *et al.* (Electrophoresis, 19(11):1862-71 (1998)) and Hancock (J. Proteome Res., 3(4):685 (2004)) as support for the assertion that "the art demonstrates that increased transcript levels do not *necessarily* correlate with increased polypeptide levels." Office Action at 4 (emphasis added).

Haynes studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See* Haynes at 1863. Haynes did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, presented herein as Exhibit 4 (Gygi *et al.*, Molecular and Cellular Biology, Mar. 1999, 1720-1730). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. *Id.* Thus, it is not clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, and Gygi reports a strong correlation between increasing mRNA levels and increasing protein levels.

The PTO focuses on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did not say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the same gene leads to a increase or decrease for the corresponding protein. Haynes did not study this issue and says absolutely nothing about it. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's position.

In the other reference cited by the PTO, a single page editorial by Hancock, the author states that it is a problem that "markers generated by proteomics are not *always* consistent with

markers that are generated from expression profiling." Hancock at 685 (emphasis added). This single sentence expressing the unsupported opinion of one scientist is relied on by the PTO to support the assertion that protein levels are not *always* correlated with transcript levels.

Read in context, it is not clear that Hancock's statement supports the PTO's conclusion. The point of his editorial is that proteomics is a developing and untested technology. After the statement quoted above, he continues: "This Editor believes that proteomics is at too early a stage for this new technology to have generated a quality list of [bio]markers." *Id.* Thus, it appears that rather than suggesting that mRNA levels are not always correlated with protein levels, Hancock is instead arguing that proteomics has not developed sufficiently to be a reliable method of generating biomarkers. And even if Hancock's statement can be read as the PTO suggest, it offers very little support since it is an opinion with no accompanying references to back it up, given in a non-peer reviewed editorial.

Based on these two references, the PTO states that increased transcript levels "do not *necessarily* correlate with increased polypeptide levels," or that "transcript levels are *not always* correlated with protein levels." Office Action at 4 (emphasis added). Even if Haynes and Hancock supported the PTO's argument, which they do not, these references do not satisfy the PTO's burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility. As stated above, the standard for establishing a use for a claimed invention is not absolute or even statistical certainty, and thus a *necessary* correlation between mRNA levels and protein levels is not required.

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (emphasis in original, internal citations omitted).

There is nothing in the cited references which cast any doubt on the Applicants assertion that in general, there is a positive correlation between changes in mRNA level and changes in the encoded protein level. To the contrary, the PTO's references support the notion that this is the working hypothesis among those skilled in the art. The fact that all of the articles cited by the PTO mention the usefulness of differential expression technology implies that there is a strong correlation between changes in mRNA levels and protein levels. As Wang states, "discovery of

differentially expressed *genes* is essential for the understanding of the molecular mechanism involved in normal and pathological states..." Wang at 276, first column (emphasis added). If there were no general correlation between changes in mRNA level and protein level, those skilled in the art would be focusing on differentially expressed *proteins* rather than differentially expressed *genes*. If there were no general correlation between changes in transcript level and protein level, differential expression of mRNA would be useless in determining the molecular basis of disease.

In further support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 5). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 6), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports

are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 7) and (4th ed. 2002) (submitted herewith as Exhibit 8)). Figure 9-2 of Exhibit 7 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 7 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 7 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 7 at 453 (emphasis added). Thus, as established in Exhibit 7, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 8, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 8 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 8 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 8 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 8 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 9) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming

majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 10. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 10 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 10 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 10 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 11, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Finally, the PTO also relies on an article by Henikoff *et al.* (Science, 278:609-614 (1997)) for the proposition that one of skill in the art would not accept homology as establishing a function for a protein. Henikoff *et al.* discusses issues associated with the classification of genes into families, including the potential classification based upon repeat motifs, modules and

chimeras within genes. While Henikoff *et al.* downplays homology as being sufficient for determining the function or biological role of a protein, this has no impact on the asserted utility of the claimed polypeptides as cancer diagnostic tools based upon differential expression data. The biological function of the PRO1753 polypeptide is not being relied on for the asserted utility. Rather, it is the overexpression of the PRO1753 gene and polypeptides in esophageal tumors compared to normal esophagus that is at issue. Thus, Henikoff *et al.* does not refute the asserted utility of the pending claims as outlined above.

Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1753 mRNA is more highly expressed in esophageal tumor compared to normal esophageal tissue, the PRO1753 polypeptide will have the same expression pattern. This differential expression of PRO1753 and related polypeptides make them useful as diagnostic tools for cancer.

*The Claimed Polypeptides would have Diagnostic Utility even if there is no Positive Correlation between Gene Expression and Expression of the Encoded Polypeptide*

Even assuming *arguendo* that, there is no direct correlation between changes in gene expression and changes in protein expression for PRO1753, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the second Grimaldi Declaration, Exhibit 5, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 12), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith (attached as Exhibit 13). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed polypeptides.

*The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"*

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d

1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed polypeptide is differentially expressed in certain tumors and that the claimed polypeptides can be used as diagnostic tools. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed polypeptides can be used as diagnostic tools for cancer, particularly esophageal cancer.

**Specific Utility**

*The Asserted Substantial Utilities are Specific to the Claimed Polypeptides*

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed polypeptides related to PRO1753. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the

PRO1753 gene and polypeptide in esophageal tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene for the PRO1753 polypeptide is expressed at least two-fold higher in esophageal tumor compared to normal esophageal tissue. These data are strong evidence that the PRO1753 gene and polypeptide are associated with esophageal tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1753 gene and polypeptide with a specific disease. The asserted utility for the claimed polypeptides as diagnostic tools for cancer, particularly esophageal tumors, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

**Conclusion**

The PTO has asserted the following arguments for why there is a lack of a substantial utility: (1) the data reporting that the PRO1753 gene is differentially expressed in certain tumors is not sufficient because there is no information regarding the absolute values of differences in transcript levels, and because the level of expression and activity or role of the PRO1753 polypeptide in cancer is not known; (2) that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue; (3) that because there is no *necessary* correlation between gene amplification and protein expression, the claimed vectors and nucleic acids cannot be used as cancer diagnostic or therapeutic tools; and (4) because mere homology does not establish the function of a protein, more research is needed to establish a utility for the claimed polypeptides. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the at least two-fold difference in expression levels, the disclosed nucleic acids and corresponding polypeptides have utility as cancer diagnostic tools. Applicants have also shown that the level of expression and activity or role of the PRO1753 polypeptide in cancer is irrelevant. Resolution of these issues is not required to use the claimed polypeptides as tumor diagnostic tools – one does not have to know why the PRO1753 polypeptide is differentially expressed in certain tumors to use it as a tumor marker.

Second, Applicants have shown that the Hu and Wang references cited by the PTO do not teach that genes or proteins differentially expressed in cancer cannot be used as diagnostic tools. In fact, neither article addresses this issue, either directly or indirectly, and they therefore offer no support for the PTO's position.

Third, Applicants have shown that the references cited by the PTO to support its conclusion that there is no *necessary* correlation between the level of gene expression and protein expression does not support the PTO's position, but in fact support the Applicant's position. Applicants submit that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reasoning or evidence to the contrary. One of skill in the art will recognize that polypeptides differentially expressed in certain cancers have utility as diagnostic tools for cancer.

Applicants have also shown that whether homology is sufficient to establish the function of a protein is irrelevant to the utility of the claimed polypeptides – utility is based on the differential expression of the PRO1753 gene and polypeptide, not their function.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because the PRO1753 gene and polypeptide are differentially expressed in esophageal tumors compared to normal esophageal tissue. This is not a general utility that would apply to the broad class of polypeptides.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be**

> **sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides relating to PRO1753 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

**Rejection under 35 U.S.C. §112, first paragraph – Enablement**

The PTO rejected Claims 1-13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

The PTO has also rejected Claims 1-5, and 12-13 as lacking enablement. According to the PTO, the specification does not enable any person skilled in the art to make and/or use the invention commensurate in scope with the claims. The PTO states that the claims are broad because they do not require the claimed polypeptide to be identical to the disclosed PRO1753 polypeptide and because the claims have no functional limitation. The PTO argues that the specification does not provide guidance for using polypeptides related but not identical to SEQ ID NO: 110. Specifically, the PTO argues that the instant specification does not identify the amino acids which are essential for its biological activity and structural integrity and those residues which are either expendable or substitutable. The PTO argues that undue experimentation would be required to make this determination in order to use the invention commensurate in scope with the claims.

As amended, the pending claims are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO: 110, and which satisfy the limitation "wherein said isolated polypeptide is more highly expressed in

esophageal tumor tissue compared to normal esophageal tissue, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples."

Applicants submit that the claimed polypeptides are enabled, as one of skill in the art would know how to make and use them. Applicants submit that it is well-established in the art how to make polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO: 110. Applicants have disclosed how to determine if the claimed polypeptides or encoding nucleic acids are differentially expressed in esophageal tumors compared to normal esophageal tissue. Applicants have also disclosed how to make antibodies to the polypeptide of SEQ ID NO: 110, and given the high amino acid sequence homology of the claimed polypeptides, one of skill in the art would know how to make antibodies to SEQ ID NO: 110 from the claimed polypeptides. Thus, one of skill in the art would know how to make the claimed polypeptides.

As discussed above, Applicants submit that they have established that one of skill in the art would believe that it is more likely than not that the PRO1753 gene and polypeptide are differentially expressed in esophageal tumors such that they can be used as cancer diagnostic tools. Given the disclosure in the specification and the level of skill in the art, a skilled artisan would know how to use the claimed polypeptides as diagnostic tools. For example, polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences and are "more highly expressed in esophageal tumor tissue compared to normal esophageal tissue..." can be used as diagnostic tools since the claimed polypeptides or their encoding nucleic acids are differentially expressed in esophageal tumors. Other claimed polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences and "said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples," are also useful diagnostic tools. Because the polypeptide of SEQ ID NO: 110 is most likely differentially expressed in esophageal tumors, antibodies for specific detection of this polypeptide in esophageal tissue samples are useful diagnostic tools.

Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

**Rejection under 35 U.S.C. §112, first paragraph – Written Description**

The PTO has rejected Claims 1-5, 12, and 13 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the claims do not require that the claimed polypeptides possess any particular biological activity, particular conserved structure, or other disclosed distinguishing feature, the claims fail the written description requirement. The PTO states that the claims are drawn to a genus of polypeptides that is defined only by sequence identity. Finally, the PTO states that the only factor present in the claim is a partial structure in the form of a recitation of percent identity. The PTO concludes that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*The Legal Standard for Written Description*

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

*The Current Invention is Adequately Described*

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching

provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

As amended, the pending claims are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO: 110, and satisfy the limitation "wherein said isolated polypeptide is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples."

Applicants maintain that there is no substantial variation within the species which fall within the scope of the amended claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO: 110. Applicants note that the pending Claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples.

In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in esophageal

tumors, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples. Like Example 14, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences will not have substantial variation.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No: 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502, which are attached hereto as Exhibits 14-19.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 110, by specifying a high level of amino acid sequence identity, by describing how to test for differential expression of the polypeptide and encoding nucleic acid, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

**Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness**

The PTO has also rejected Claims 1-6, 9, 10, 12, and 13 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the recitation of "extracellular domain" and "the extracellular domain...lacking its associated signal sequence" because a signal sequence is not generally considered part of an extracellular domain.

Applicants have amended the claims to delete any reference to an extracellular domain. In light of these amendments, Applicants request that the PTO withdraw the indefiniteness rejections under 35 U.S.C. §112, second paragraph.

## CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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